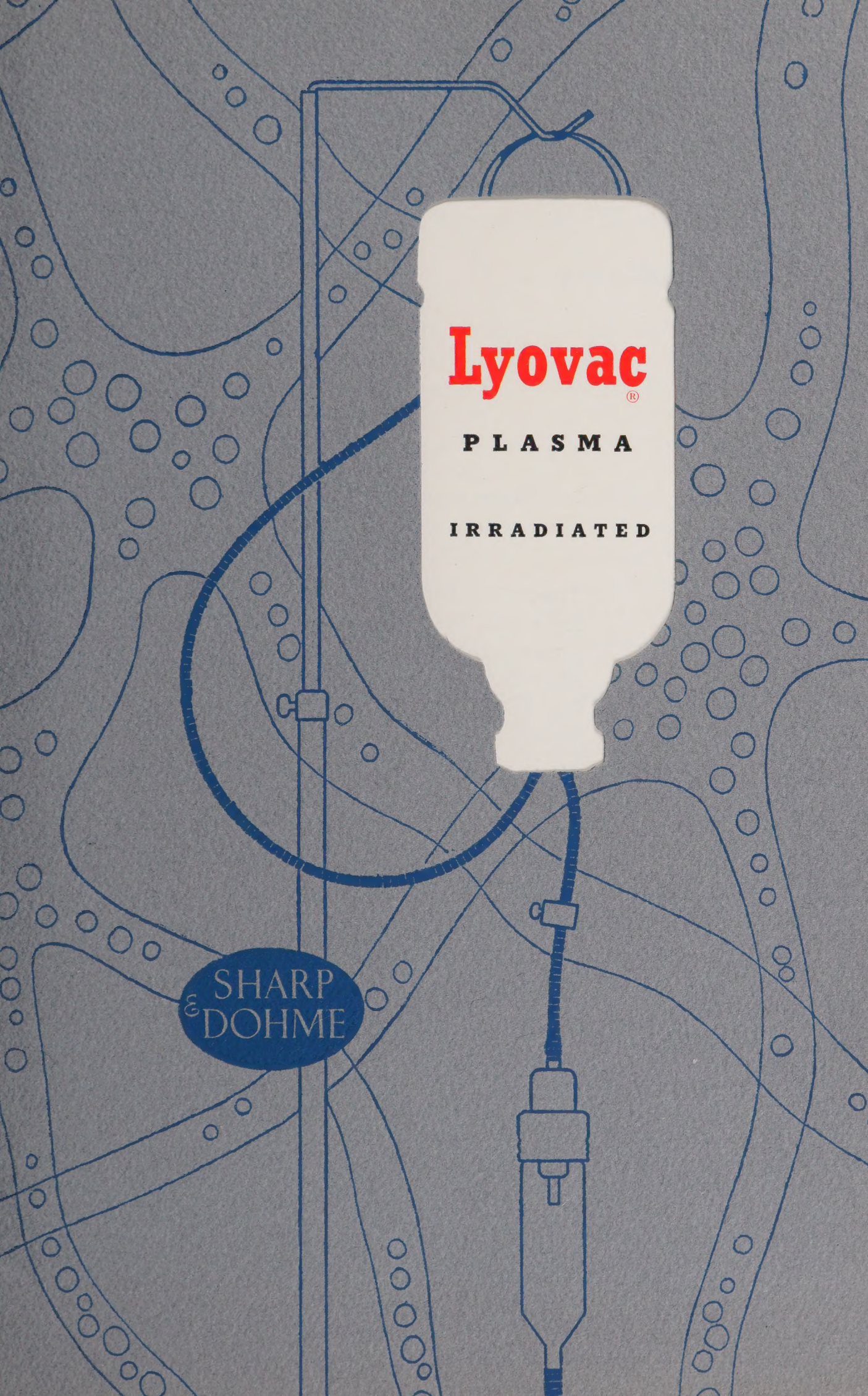


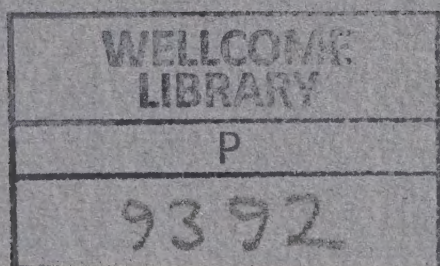
The image shows a white, pear-shaped blood bag with a blue line drawing of a tube and needle attached. The bag is centered against a grey background with a blue line drawing of a network of vessels and small circles. The text 'Lyovac' is in red, 'PLASMA' is in black, and 'IRRADIATED' is in black. The Sharp Dohme logo is in a blue oval at the bottom left.

Lyovac[®]

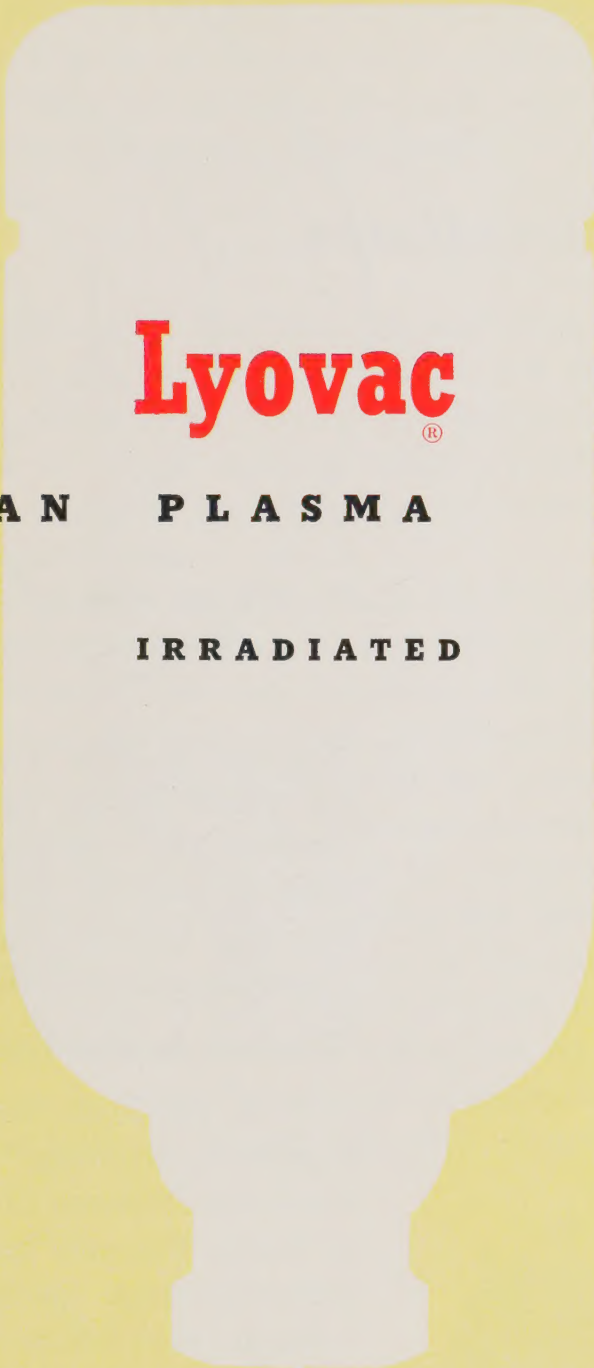
P L A S M A

I R R A D I A T E D

**SHARP
DOHME**



22502624050



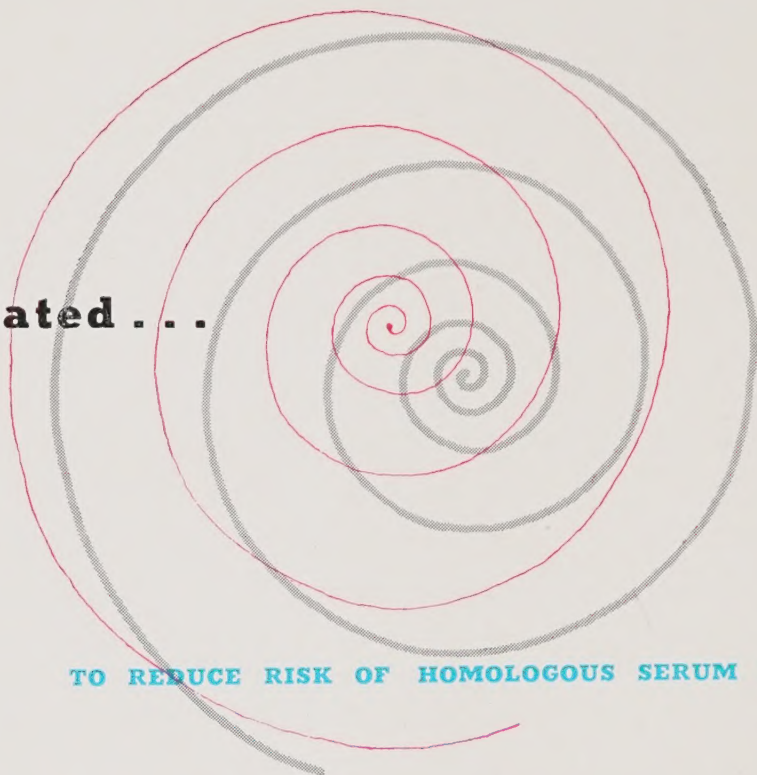
Lyovac[®]

N O R M A L H U M A N P L A S M A

I R R A D I A T E D

SHARP
& DOHME

now irradiated . . .



TO REDUCE RISK OF HOMOLOGOUS SERUM HEPATITIS!

The rationale for the use of plasma as a substitute for whole blood has been established by many workers, particularly for such indications as shock with or without hemorrhage,^{1,2} burns,^{3,4} restoration and maintenance of body proteins,³ and for the emergency treatment of severe hemorrhage.^{1,2,3}

Clinical Indications

SHOCK: In shock, the marked fall in blood pressure with resultant failure in circulation results from the decrease in blood volume due to the loss of fluids through the capillary walls into extravascular tissue spaces. Since plasma proteins are colloidal and diffuse slowly, they are not lost from circulation as readily as crystalloids. Plasma may, therefore, be used more effectively to regulate and maintain blood volume.⁵



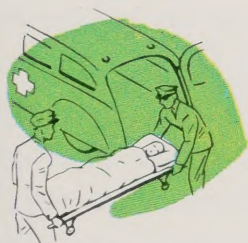
BURNS: In severe or extensive burns there is a marked loss of fluid containing large amounts of plasma proteins. This loss is further enhanced by the increased capillary permeability throughout the entire body due to the liberation of toxic substances from the burned area. As a result,



there occurs blood concentration with decrease in blood volume and circulatory failure. It is stated³ that the red blood cell count may increase to 8,000,000 or more per cubic millimeter. Because of this, transfusion of whole blood is contraindicated if plasma is available.

HEMORRHAGE: It has been shown⁶ that the important factor in hemorrhage is not primarily the actual loss of red blood cells, but is rather the decrease in blood volume, which causes a drop in blood pressure and ultimate circulatory failure and tissue anoxia.

It is therefore essential that the blood volume be reestablished as soon as possible following the hemorrhage. This may be done with the least loss of time through the use of prepared plasma, which may be administered in the home or hospital immediately. After the acute emergency has been met, whole blood may be transfused, but this is rarely necessary unless the hemoglobin falls below 6 Gm. per 100 cc. or the number of red blood cells is less than 2,000,000 per cubic millimeter. An additional indication for the use of plasma is in the treatment of excessive hypoprothrombinemia associated with anticoagulant therapy.^{7,8}



HYPOPROTEINEMIA: When protein intake is insufficient, or chronic loss of protein occurs, a reduction in plasma protein results. If the protein content of the plasma falls below 4 per cent, fluid is lost from the capillaries and tissue edema results. Treatment should therefore attempt to restore the normal protein content of the plasma.

In cases uncomplicated by nephritis, marked diuresis and dramatic clearing of the edema frequently follow the administration of sufficient amounts of plasma.



Clinical Indications in Pediatrics



In addition to its value in the treatment of shock, burns, hemorrhage and hypoproteinemia as outlined above, plasma has other uses in pediatrics.

Plasma is recommended both for the prophylaxis and the treatment of circulatory failure in children, being equally as effective as whole blood in increasing the blood volume.⁹ The therapeutic effectiveness of plasma has been demonstrated also in the treatment of dehydration and intoxication in infants and children,¹⁰⁻¹² and in the therapy of neonatal diarrhea.¹³⁻¹⁶

How Prepared

It is generally recognized that some samples of human blood contain a virus capable of causing so-called serum hepatitis or serum jaundice following transfusion.¹⁷ Although the relationship of homologous serum hepatitis to infectious hepatitis is not entirely clear, present indications are that the icterogenic agent of both diseases is a virus. The reported morbidity rate of serum hepatitis has been approximately 4.5 per cent in patients who have received pooled plasma collected during World War II.¹⁸ Despite careful selection of blood donors under strict supervision, there is still the possibility that some blood will contain the hepatitis virus, since no laboratory procedure exists for its detection in the blood.

Recently, methods have been developed for the sterilization of suspensions containing bacteria and viruses.¹⁹⁻²¹ In controlled studies carried out in human subjects the development of hepatitis was prevented in those individuals who received injections of irradiated human serum.^{21,22} Toxic effects due to irradiation of plasma were not observed following injection of this material and there was no deleterious effect on the therapeutic value of the plasma.^{21,23}

More recently several cases of hepatitis have occurred following administration of irradiated

Effect of Irradiation of Serum Contaminated with S-H Virus on Incidence of Hepatitis*

	Number	Amount of Serum Administered	Route	Hepatitis	
				Number	%
Control Group	11	4 cc.	Intramuscular	6	47
	4	2 cc. serum + 10 cc. convalescent plasma	Intramuscular	1	
Irradiated Serum Group	11	7 cc.	Intramuscular	0	0.0

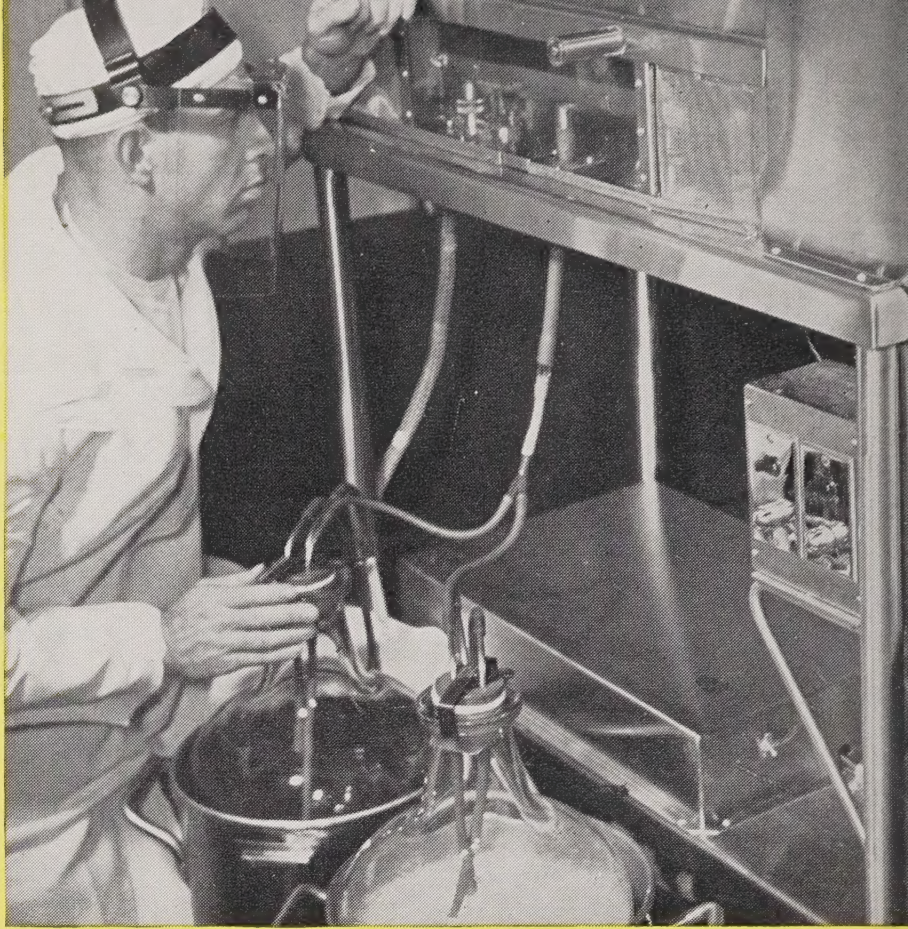
Note that in control group of 15 volunteers, inoculated with human serum known to be contaminated with virus S-H, 7 developed hepatitis. The same contaminated serum was irradiated and administered in large amounts to 11 individuals. None developed hepatitis.

* Adapted from table in J.A.M.A. 138:341, Oct. 2, 1948

human plasma in which, despite other well recognized sources of infection,²⁴⁻²⁶ the question was raised whether the virus was transmitted through the plasma. The best reply to this question is that, based on present knowledge and experience and on the report of Blanchard and his associates,²¹ ultraviolet irradiation of plasma would appear to reduce substantially, if it does not entirely obviate, the danger of a recipient acquiring homologous serum hepatitis.

Accordingly, in the preparation of 'Lyovac' Normal Human Plasma (Irradiated) ultraviolet irradiation is employed as an additional protection against bacterial or viral contaminants that, in spite of all precautions, may be present.

A stainless steel roller, rotating at a constant speed, dips into a pan of pooled blood plasma and picks up a thin film of the plasma on its curved surface. As the drum turns, the plasma film is exposed to ultra-violet irradiation from a bank of 18-watt, cold quartz lamps, and is then removed by a flexible wiping blade and conveyed to a sterile container for quick freezing and vacuum drying (lyophile process).



'Lyovac' Normal Human Plasma (Irradiated) is prepared from fresh human citrated blood. Each donor is examined before being bled and must show negative serologic tests in accordance with the requirements of the National Institute of Health.

The plasma is pooled and is frozen rapidly at very low temperatures and dehydrated from the frozen state under high vacuum. The resulting product is then sealed under vacuum in a bottle.

The advantages of plasma prepared by this special process are (a) that the period of preservation is extended over a period of 8 years,²⁷ and (b) the protein patterns of the lyophilized plasma differ little from those of the fresh liquid plasma, indicating that the lyophile technic causes little or no denaturation of the proteins.²⁸

The colloid osmotic pressure of restored 'Lyovac' Normal Human Plasma (Irradiated) is

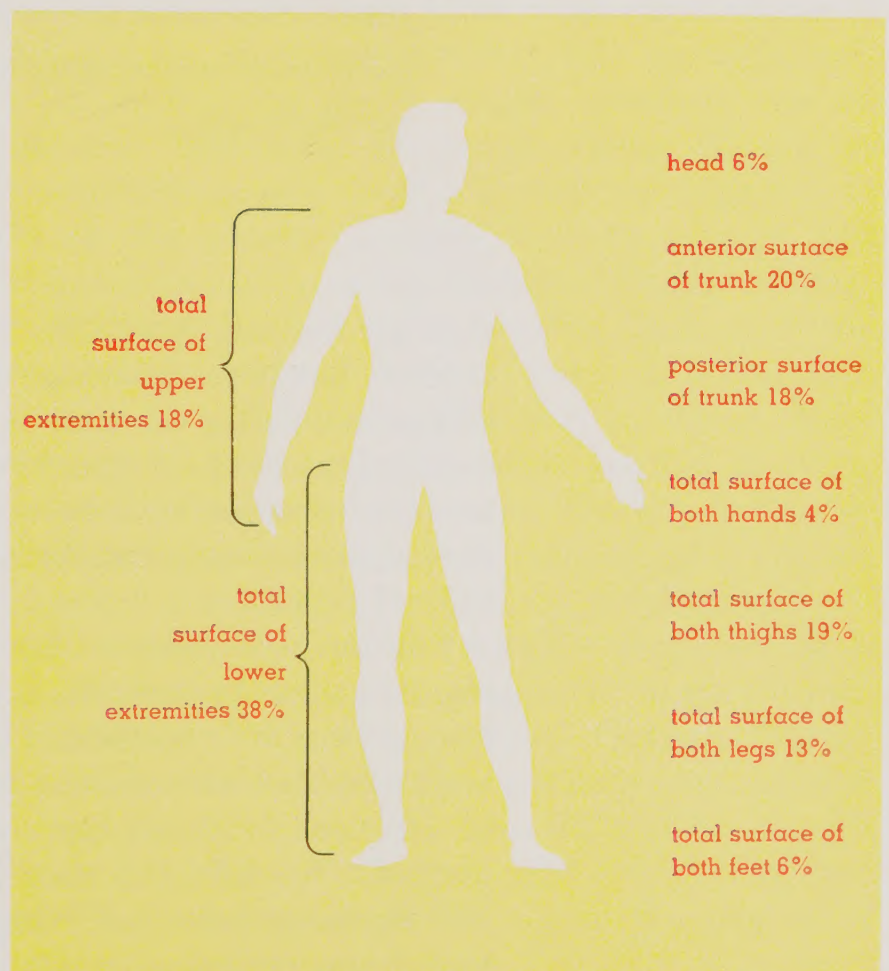
approximately equivalent to twice its volume of whole blood. The content of complement, antibodies and coagulating elements is essentially the same as that of the original fresh blood.

Dosage and Administration

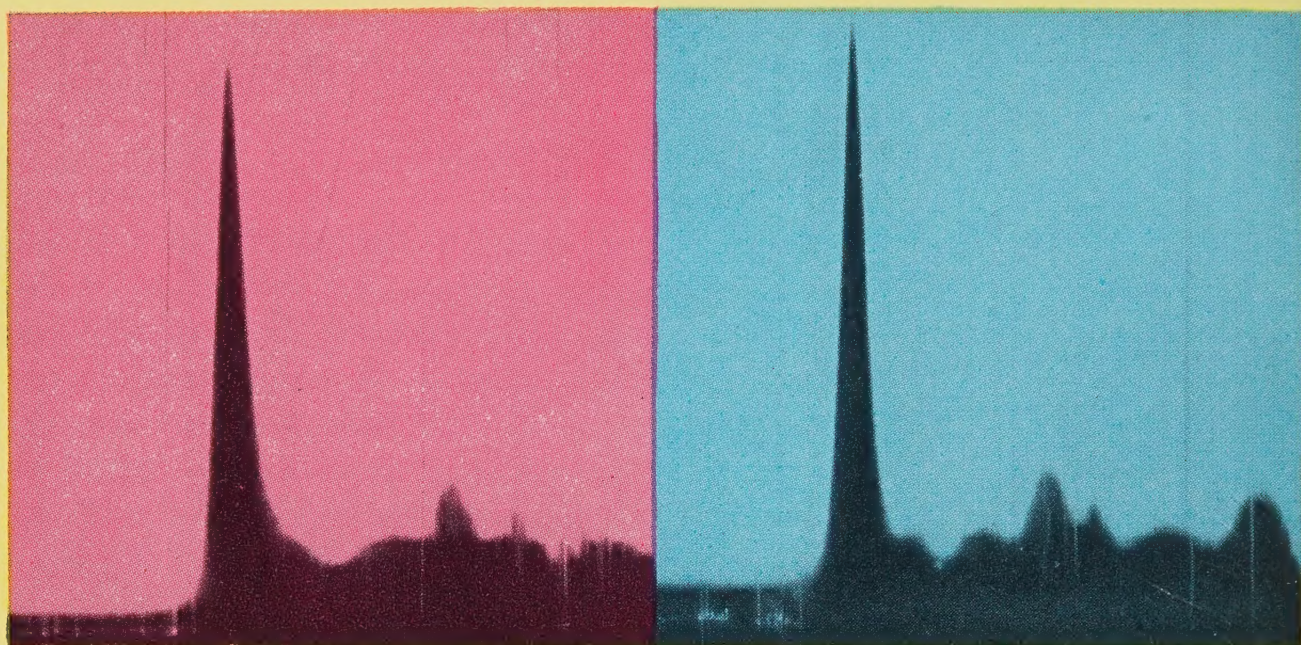
'Lyovac' Normal Human Plasma (Irradiated) is administered intravenously at a rate of 40 to 60 drops per minute. In emergency the rate may be increased without reaction. When impossible to administer plasma by vein, it may be introduced into the marrow cavity of the sternum, using a suitable sternal puncture needle provided with a stylet. In some instances, plasma may be administered intramuscularly.

It has been concluded as a result of clinical trial and field use by the armed forces that plasma dosage, in general, has been inadequate. In the

**Relative
skin areas
according
to Berkow:**



Electrophoretic Patterns of Irradiated and Nonirradiated Normal Human Plasma



Irradiated Plasma

Nonirradiated Plasma

Note that there is no significant alteration in electrophoretic patterns of irradiated and nonirradiated normal human plasma. Also there is no significant change in prothrombin complement, gamma globulin and other recognized plasma constituents.

average clinical condition where plasma is indicated it has been determined that 500 cc. instead of the usual 250 cc. unit is most beneficial. Because of the need for standardizing plasma dosage, several formulas have been suggested in order to determine the amount of plasma required for any individual case.

For the treatment of burns, the National Research Council's formula is simple to apply. Following Berkow's method,²⁹ the extent of the burn is determined and plasma is injected at the rate of 100 cc. for each per cent of body surface burned. One-half the dose is given immediately and the remainder in divided doses over a twenty-four hour period.

One note of considerable importance has been advanced by the Conference on Burns, National Research Council, namely, that the amount of sodium chloride solution injected in any twenty-four hour period, for the first few days after the burn, should not exceed the amount of plasma administered during that period.³⁰

Harkins, Lam and Romence³¹ utilize a simple method using the hematocrit for determination of hemoconcentration. One hundred cubic centimeters of plasma are administered for each 0.1 per cent the hematocrit exceeds the normal of 45.

As much as 4,000 cc. of plasma have been administered in a single dose, and 36,000 cc. of plasma have been used in an individual patient over a period of time.³²

Dosage and Administration in Pediatrics

In pediatric use no definite dosage schedule can be outlined, as the factors of age, sex, weight, condition and response of the patient must be taken into consideration. In most cases, doses of 50 cc., or multiples thereof, will be sufficient.

In hypoproteinemic states, whether due to chronic infections, nephrosis, celiac disease or malnutrition, the dosage should be adjusted to bring the plasma protein level to normal and thus maintain physiologic levels of plasma protein.

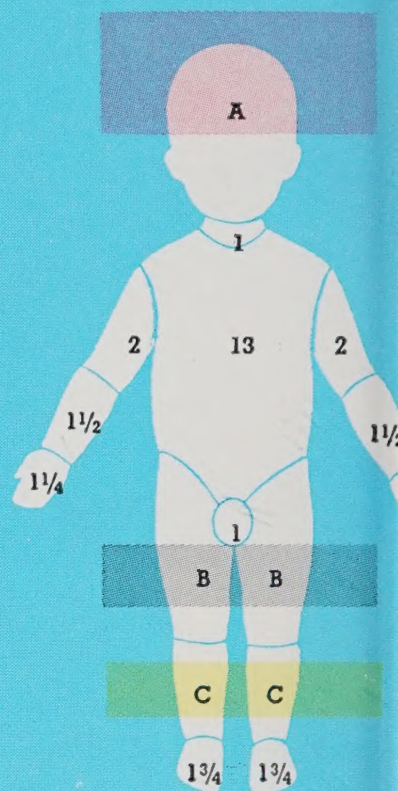
For the treatment of infectious diarrhea of the newborn, an initial dose of 50 cc. of lyophilized plasma is administered followed by 25 cc. daily for three or four days of either normal or twice normal concentration plasma. Twenty-five cubic centimeters of plasma of normal concentration are injected daily for three days for prophylaxis.

In certain conditions, notably nephrosis, it is desirable to administer plasma in more concentrated form. 'Lyovac' Normal Human Plasma (Irradiated) lends itself particularly well to such use as it may be restored to as little as one-fourth of its original volume. A longer restoration time will be required depending upon the degree of concentration employed.

DOSAGE AND ADMINISTRATION OF PLASMA IN EMERGENCY TREATMENT OF BURNS

DOSAGE: 100 cc. of plasma for each per cent of body surface burned to all patients with 10 per cent or more area burn. One-half the dose is given in first 4-6 hours, one-quarter in next 6 hours and remainder in next 12 hours.

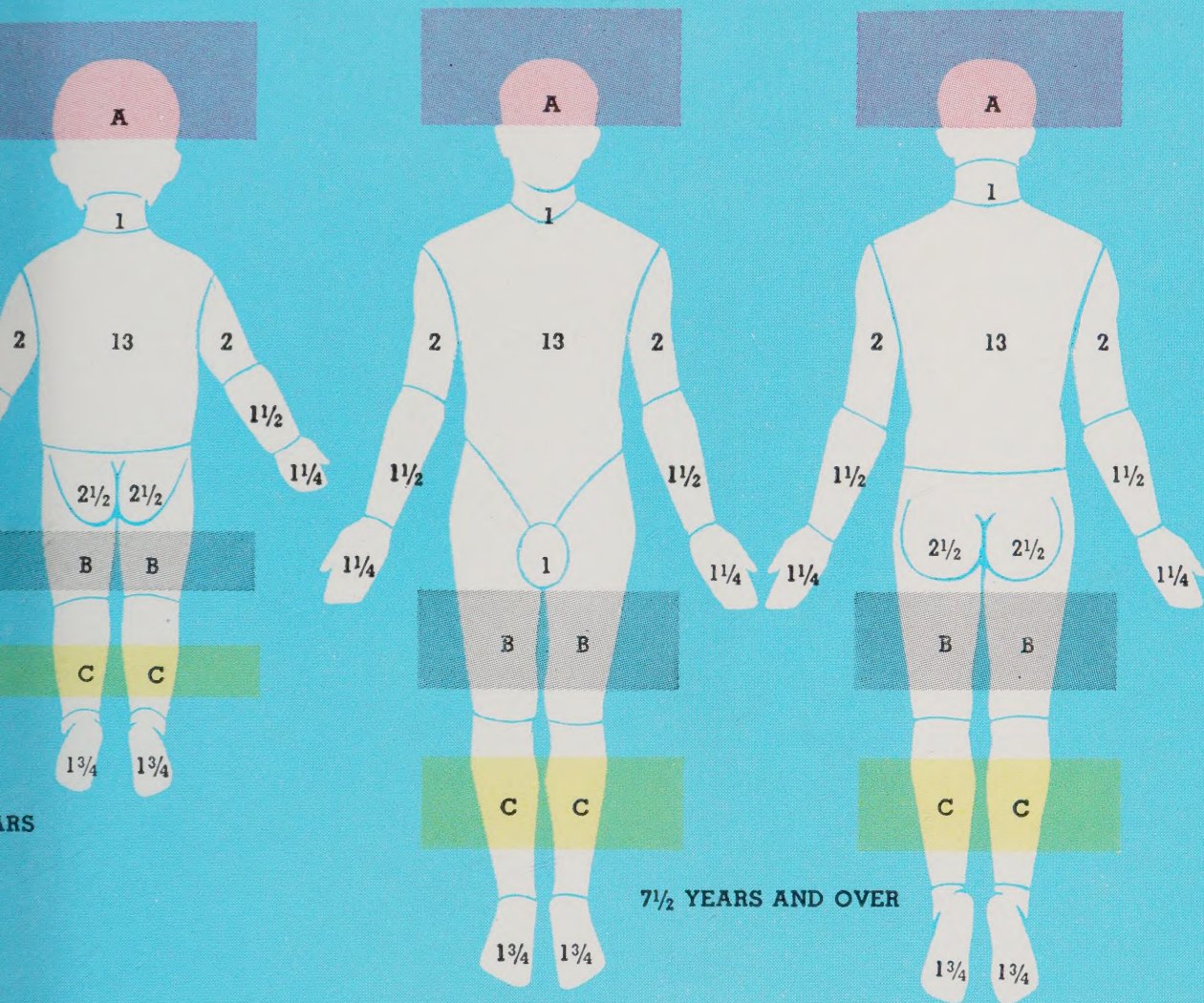
ADMINISTRATION: 'Lyovac' Normal Human Plasma Irradiated is administered at rate of 40-60 drops per minute. In emergency, this rate may be increased without reaction.



BIRTH

AREA	
A	= 1/2 of Head
B	= 1/2 of One Thigh
C	= 1/2 of One Leg

Estimate of Per Cent of Burn Area*



Relative Percentages of Areas Affected by Growth

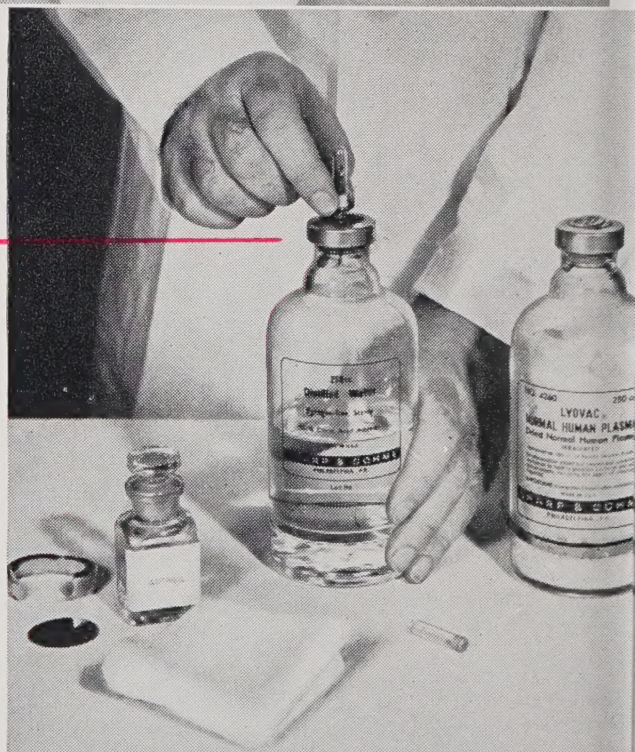
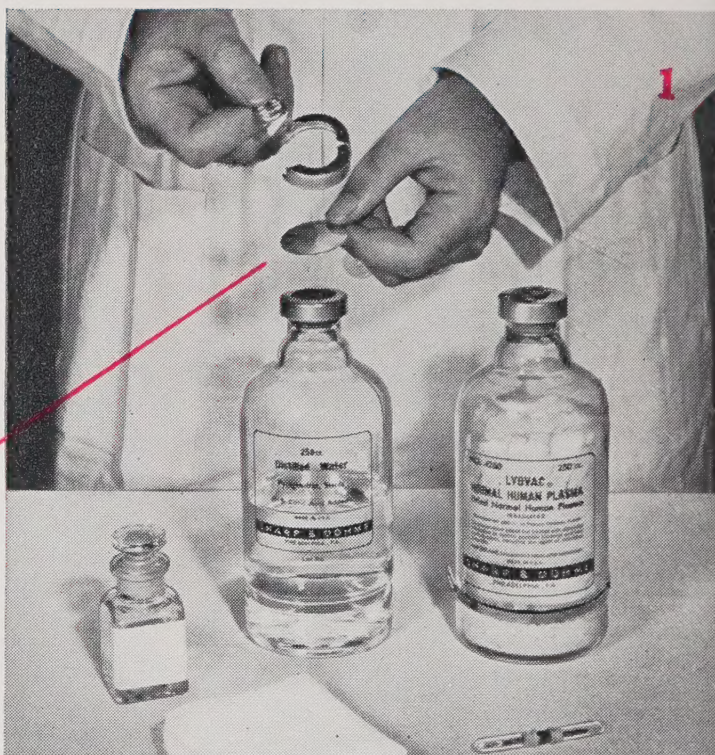
AGE 0	1	5	10	15	ADULT
9 1/2	8 1/2	6 1/2	5 1/2	4 1/2	3 1/2
2 3/4	3 1/4	4	4 1/4	4 1/2	4 3/4
2 1/2	2 1/2	2 3/4	3	3 1/4	3 1/2

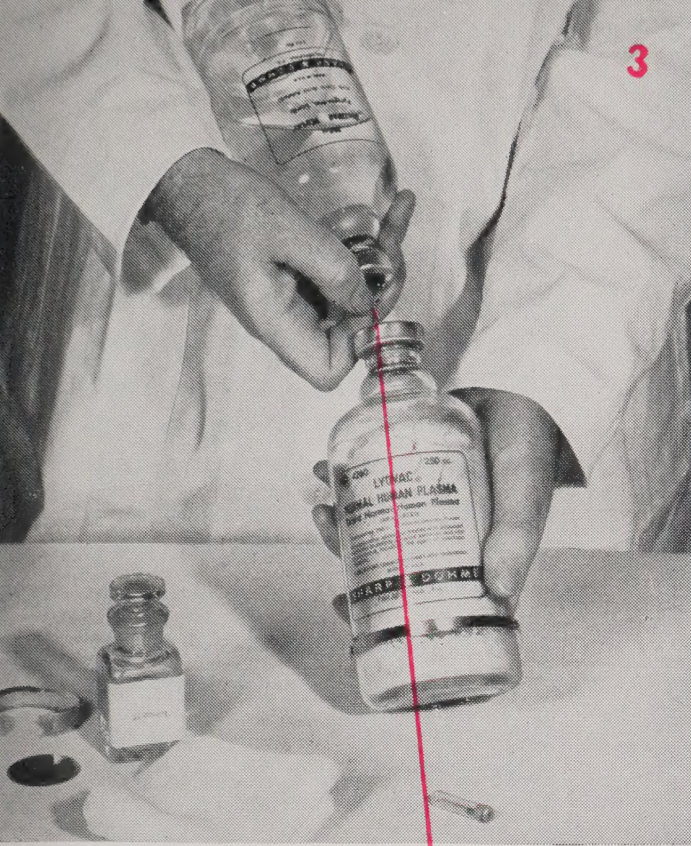
*Reproduced through courtesy of Dr. Charles C. Lund and Surgery, Gynecology and Obstetrics

Directions for Restoration and Use for 250 cc. and 500 cc. units

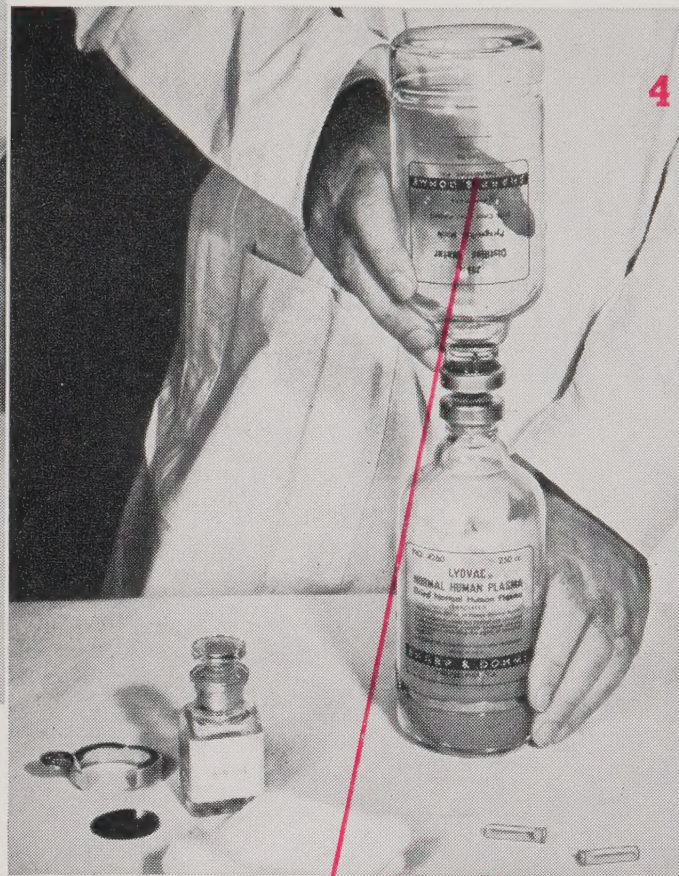
'Lyovac' Normal Human Plasma (Irradiated) is packaged under high vacuum. Guard against breakage and loss of vacuum before restoration. To restore the 'Lyovac' plasma to the liquid form, observe carefully the following steps:

1. Lift up and tear off the central aluminum disc of the closure on the bottle of diluent. Remove the inner aluminum disc Fig. 1. Swab the exposed rubber surface with alcohol. Remove one of the glass caps with its rubber washer from the double-pointed needle. Insert this exposed end of the needle through the center of the stopper in the bottle of the diluent Fig. 2.





2. Lift up and tear off the central aluminum disc of the closure on the bottle of plasma. Remove the inner aluminum disc and swab the exposed rubber surface with alcohol. Remove glass cap from the upper end of the double-pointed needle now seated in the stopper of the diluent bottle. Hold the bottle of plasma in one hand, invert the bottle of diluent in the other hand, and push the exposed end of the needle through the center of the stopper Fig. 3, making



certain that the diluent is always above the bottle of plasma Fig. 4. There is sufficient vacuum in the bottle to draw in all the diluent.

3. Withdraw the empty diluent bottle from the end of the needle and in a few seconds, when the vacuum has been satisfied completely, remove the needle itself. Gentle agitation will help restoration to the fluid state, which usually is complete within five minutes.

4. Suspend the bottle of re-stored plasma by means of metal hanger provided Fig. 5.

5. The short rubber tubing has an air filter at one end; hang this end on the suspending metal hanger. Remove the glass cap from the needle on the opposite end, and insert the needle through the rubber stopper of the bottle Fig. 6.

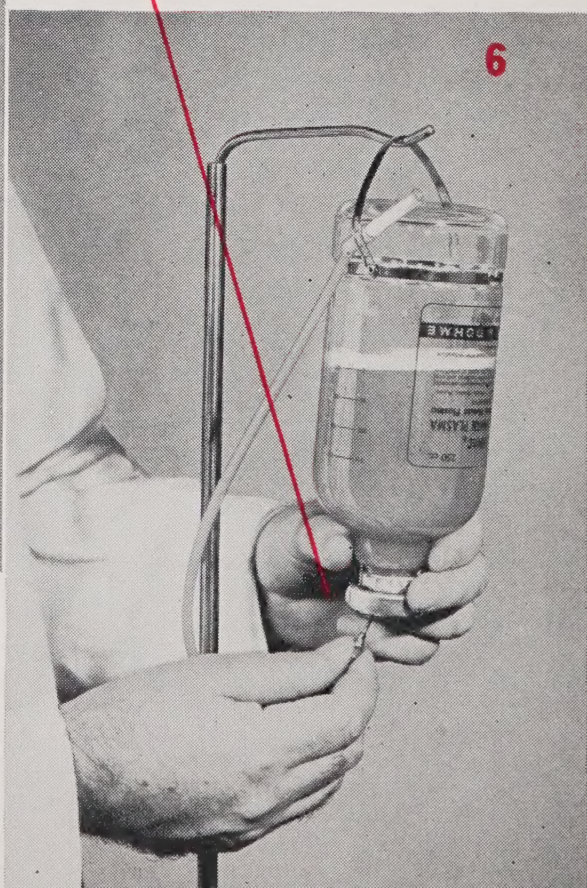
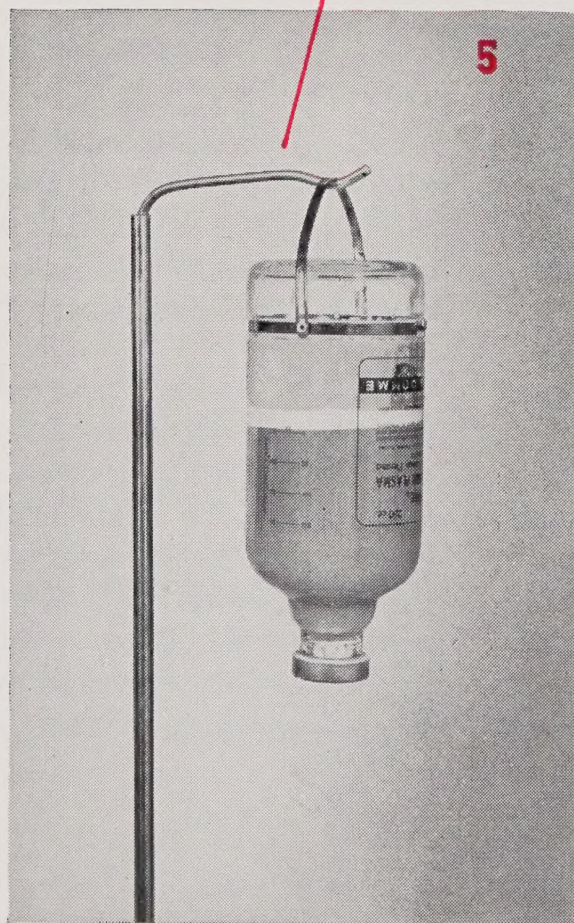
6. Prepare the sterile intravenous equipment as follows:
(1) tighten the screw clamp;
(2) examine all connections

of the filter, which must fit tightly to avoid leakage; (3) remove glass cap and stylet from the connecting needle attached to the tubing above the screw clamp, and insert this needle through the rubber stopper of the bottle and in the opposite direction to the air filter needle.

7. Remove the paper covering from the sterile glass needle adapter at the opposite end of the long rubber tubing.

8. Remove the intravenous needle from its protective container, and connect this needle to the glass adapter.

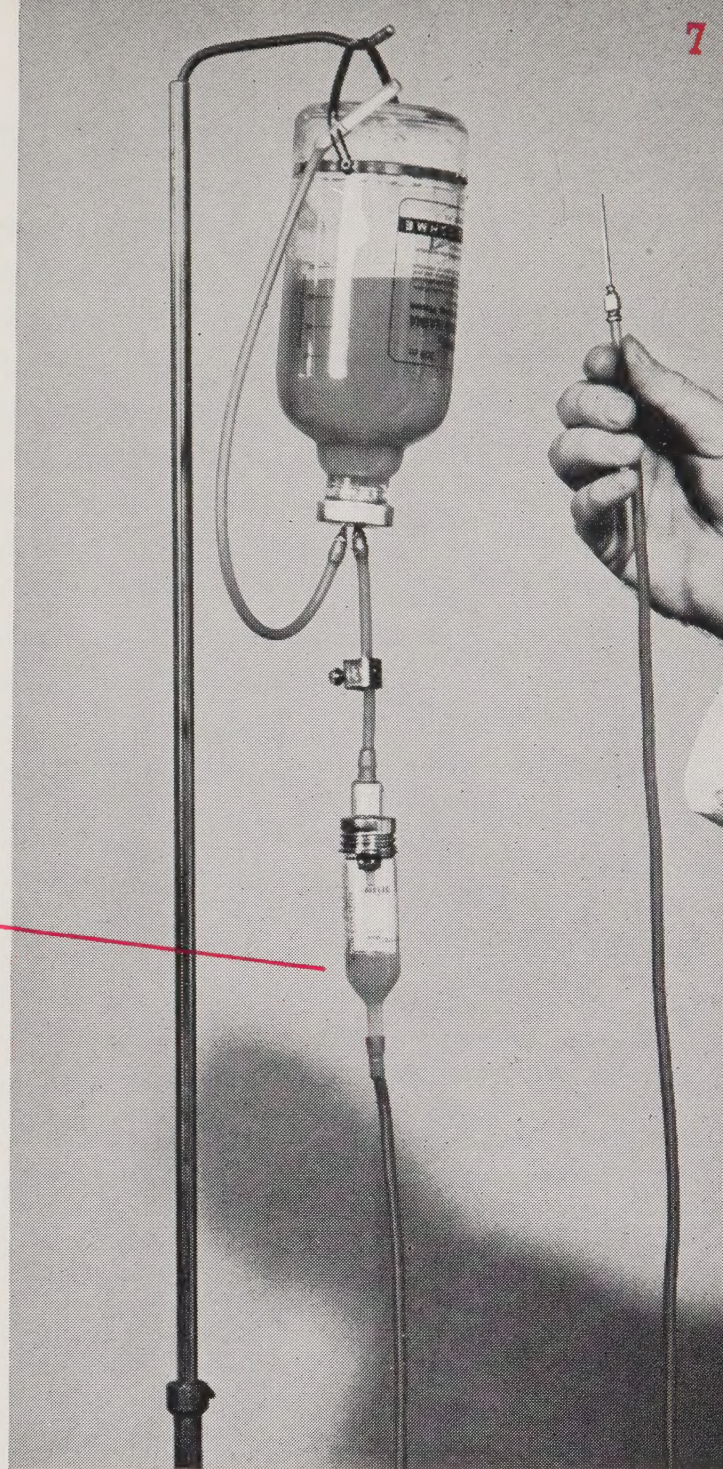
9. Remove the glass cap from the intravenous needle. Displace the air in the entire in-



travenous equipment. To do this, hold the injecting needle end of the tubing above the level of the plasma in the bottle, and open the screw clamp. The plasma will then run in to fill the tubing and needle. Lower the needle end of the tubing to expel air bubbles. Again raise and lower the needle end of the tubing until all air bubbles are expelled. When the plasma filter and the adjustable flow control are used, raise the needle end above the level of the plasma until the flow control is filled up to the mark Fig. 7.

10. Pinch the tubing between the fingers or tighten the clamp while the needle is being inserted into the vein.

When satisfied that the needle is properly in the vein, slowly release the tubing or loosen the clamp and regulate the rate of flow by adjusting the clamp.



Directions for Restoration and Use for 50 cc. unit

It is recommended that the following steps be observed carefully in using the accompanying package:

1. 'Lyovac' Normal Human Plasma (Irradiated) in the 50 cc. package is restored as described under directions 1, 2 and 3 for the 250 cc. and 500 cc. units.

2. When restoration is complete, the plasma is ready for injection. When ready to give the injection, a sterile syringe of large size (25 or 50 cc.) must be provided. The restored human plasma can then be removed from the bottle with the same technic as commonly used with any rubber-stoppered container.

An 18-gauge needle is satisfactory for most intravenous injections although small sizes are required in infants and small children. Set the plunger in the syringe at the volume to be withdrawn and insert the needle through the center of the rubber stopper and inject into the bottle the amount of air equivalent to the volume of plasma to be withdrawn.

3. Then, with the bottle uppermost, draw back on the syringe plunger and fill the syringe with the restored human plasma. The filled syringe is now ready for use.

4. The needle is then inserted into the vein through the previously cleansed site and the plasma injected slowly.

NOTE: If the vacuum in the bottle of plasma should be lost inadvertently, the diluent may be withdrawn by means of a syringe and injected directly into the bottle of plasma.

Cleaning the Equipment for Re-use

The equipment for intravenous injection may be used a second time if the following precautions are taken:

The equipment should be disconnected and the separate parts handled as follows. All the rubber tubing should be rinsed immediately in cool water and placed in boiling water for a few minutes, then rinsed again in pyrogen-free, distilled water and dried.

All glass and metal parts, i.e., needles and glass adapter, should be rinsed thoroughly in cool water, then boiled in distilled water containing a small amount of washing soda (2 ounces per quart).

The parts are then rinsed in distilled water, dried and reassembled. The entire outfit may then be sterilized by autoclaving at fifteen pounds pressure for fifteen minutes.

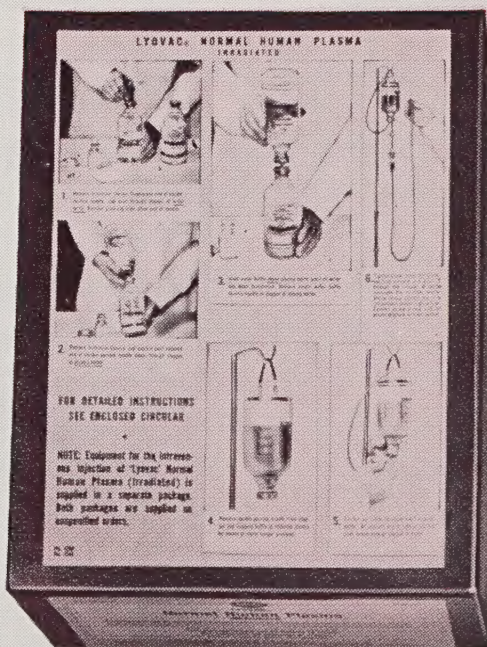
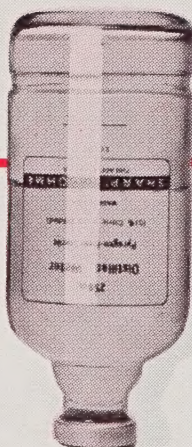
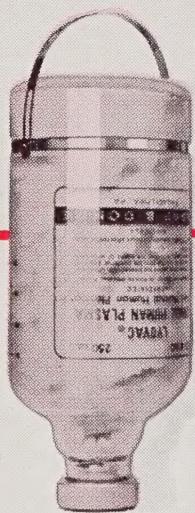
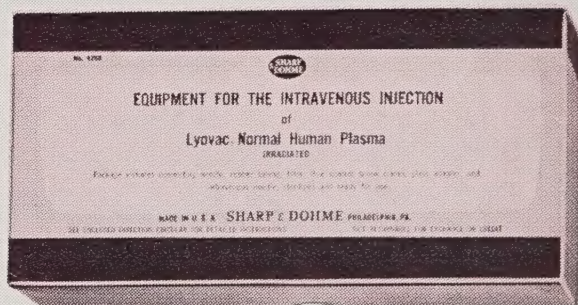
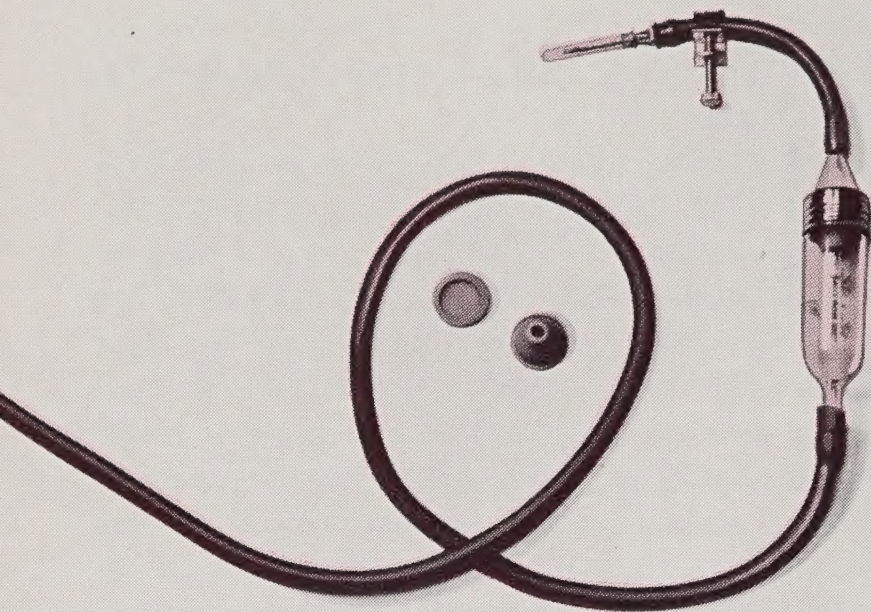
Rubber tubing and collar-washers as now supplied will withstand one or at most two sterilizations by autoclave. A duplicate set of rubber collar, washer and steel filter is included with the outfit. Other parts of the outfit may be used repeatedly by following the above directions and by giving special attention to the plasma filter. This filter should be taken apart and the stainless steel filter screen, after removing it from the rubber collar-washer, should be immersed in dilute nitric acid or a solution of hydrogen peroxide for a few minutes and then rinsed well. After a final rinsing in pyrogen-free, distilled water all the parts are dried, reassembled and sterilized by autoclaving at fifteen pounds pressure for fifteen minutes.

Precautions

'Lyovac' Normal Human Plasma (Irradiated) complies with the regulations of the National Institute of Health with regard to dating and moisture content. It should be kept at a temperature not exceeding 37 C. (98.6 F.), and, if facilities are available, preferably in a cool place.

Plasma need not be warmed to body heat before administering it, nor should an attempt be made to warm the solution during administration. Proper temperature for injection is best attained by gently warming the diluent to body temperature (not above 37 C.) before restoration.

The pyrogen-free, sterile, 0.1 per cent citric acid solution supplied is the best diluent for restoring 'Lyovac' Normal Human Plasma (Irradiated). Normal saline or glucose solutions may be used for this purpose at the discretion of the physician, but Ringer's solution must never be used since the excess of calcium will cause a precipitation of the fibrin from the plasma.



**SHARP
& DOHME**

How Supplied

No. 4265—'Lyovac' Normal Human Plasma (Irradiated) is supplied in a package containing one bottle, with vacuum-tight closure, representing 50 cc. of pooled original plasma, which is restored to full volume by adding 50 cc. of sterile, pyrogen-free, 0.1 per cent citric acid solution contained in the accompanying bottle, together with double-pointed connecting needle.

No. 4260—'Lyovac' Normal Human Plasma (Irradiated) is supplied in a package containing one bottle, with vacuum-tight closure, representing 250 cc. of pooled original plasma, which is restored to full volume by adding 250 cc. of sterile, pyrogen-free, 0.1 per cent citric acid solution contained in the accompanying

bottle, together with double-pointed connecting needle and air filter.

No. 4263—'Lyovac' Normal Human Plasma (Irradiated) is supplied in a package containing one bottle, with vacuum-tight closure, representing 500 cc. of pooled original plasma, which is restored to full volume by adding 500 cc. of sterile, pyrogen-free, 0.1 per cent citric acid solution contained in the accompanying bottle, together with double-pointed connecting needle and air filter.

No. 4268—Equipment for Intravenous Injection:

This package consists of connecting needle, rubber tubing, filter, flow control, glass needle adapter and intravenous needle, sterilized and ready for use.

This product is to be used only by or under the direction of a physician.

Sharp & Dohme • Pharmaceuticals

Biologicals

Philadelphia 1, Pa.

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